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EDITORIAL COMMENT

Eliminating Right-to-Left Shunt With Patent Foramen Ovale Closure

Not as Simple as it Seems*

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Patent foramen ovale (PFO) is associated with numerous clinical conditions, such as cryptogenic stroke, paradoxical embolism, migraine headaches, decompression illness, and shunt-related hypoxemia. As a result, transcatheter closure of PFO has become relatively common, driven by the apparent ease of the procedure, patient and clinician preference over medical therapy, and numerous retrospective analyses demonstrating clinical benefit. The procedure is performed under conscious sedation and, in experienced hands, can been done routinely in under 30 min. The fact that there have been no large prospective randomized trials to prove the efficacy of PFO closure has done little to dissuade the enthusiastic use of closure devices.

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The immediate and long term goal of transcatheter PFO closure is elimination of right-to-left shunt (RLS) through the interatrial septum. When detected, RLS is generally secondary to an atrial level shunt (i.e., PFO), but noncardiac RLS (primarily intrapulmonary) has also been implicated in the pathophysiology of clinical conditions resulting from paradoxical embolism (1). Intrapulmonary RLS can coexist with PFO and in some cases can be mistaken as a source of RLS in a patient presumed to have a PFO. For instance, in the MIST (Migraine Intervention With STARFlex Technology) trial, 5 of the 74 patients with RLS randomized to PFO closure actually had no PFO found at the time of the procedure. The cause of the RLS in these patients was presumably due to an intrapulmonary shunt (2). The presence of coexisting intrapulmonary shunting would clearly have major implications when designing trials to assess the efficacy of PFO closure to eliminate RLS. Methods to identify these confounding patients have not been well-described in published reports to date.

Jesurum et al. (3), in this issue of *JACC: Cardiovascular Interventions*, describe a novel method to assess the prevalence of secondary (intrapulmonary) RLS in patients undergoing transcatheter closure of PFO. During sizing-balloon inflation within the PFO (and presumed occlusion of the PFO due to lack of color flow seen with intracardiac echocardiography [ICE] around the balloon), agitated saline was injected into the inferior vena cava with calibrated respiratory strain, followed by assessment of RLS via transcranial Doppler (TCD). If >10 embolic tracks were detected, this was defined as a "secondary RLS." After PFO closure, residual RLS was assessed immediately with agitated saline and TCD and in late follow-up with TCD and transthoracic echocardiography. This study demonstrated that those subjects with RLS during balloon inflation (secondary RLS) were significantly more likely to have RLS during immediate and late follow-up when compared with those patients without RLS during balloon inflation. Patients with secondary RLS also had more atrial septal aneurysms (p = NS) and significantly larger PFO waist diameters than those without secondary RLS ($p = 0.013$). With these data, the authors concluded that ICE, TCD, and balloon occlusion can be used to detect secondary RLS during PFO closure.

The overall concept of this report is novel, because there have been no previous reports using this technique (or any other for that matter) to assess the prevalence of secondary RLS during PFO closure. The authors are to be congratulated for attempting to broaden our understanding of RLS physiology in a PFO-closure population. However, as with all complex questions, the devil is ever present in the details. First, the title and claim that persistent shunt after balloon occlusion or in follow-up is due to a "secondary source of RLS" is presumptive. Certainly, some of the patients might have a coexisting intrapulmonary shunt. However, another quite plausible explanation is that those patients with secondary RLS at baseline actually had incomplete occlusion of the PFO with the sizing-balloon. Even in the absence of color flow on ICE, it might be impossible to rule out small areas on the edge of the balloon (or associated microfenestrations) where bubbles could cross. Also, the balloon might appear occlusive at rest although not be occlusive with increased right-sided pressure during respiratory strain. The fact that the secondary RLS group had more atrial septal aneurysms and a larger balloon waist diameter would also suggest that incomplete balloon occlusion of large, floppy PFOs is a more likely source of RLS than an intrapulmonary etiology.

Improved methodology might include the use of transesophageal echocardiography or other imaging of the left atrium and pulmonary veins during balloon occlusion of the

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PFO, in an effort to document that bubbles emanate from 1 of the pulmonary veins and not from the interatrial septum. At follow-up, the authors did not comment on the timing of the appearance of saline contrast in the left atrium as assessed by transthoracic echocardiography. Whereas there are data showing that pulmonary arteriovenous malformations (PAVMs) and intracardiac RLS do overlap in the time delay during which the bubbles appear in the left atrium (4), one might expect a trend toward earlier detection in those with persistent cardiac shunts. Documenting PAVMs with pulmonary angiography in patients with large secondary RLS would add strength to the authors' conclusions. The majority of PFO closures in this series were performed with the CardioSEAL device, and the high persistence of late shunt (44%) in those subjects without secondary RLS suggests that at least some of the persistence of late shunt is device-related and not intrapulmonary. Finally, the clinical significance of these secondary shunts remains unclear, because this study was not powered to evaluate clinical event rates in the 2 groups.

In conclusion, Jesurum et al. (3) report that secondary RLS are common (20%) in patients referred for transcatheter PFO closure. This would make intrapulmonary shunting almost as common as PFOs are in the normal population. If PAVMs, albeit small, are actually this common, then that finding is in itself new and unexpected. In an autopsy study from Johns Hopkins Hospital, only 3 PAVMs were detected in 15,000 consecutive autopsies (5). Many of the angiographic studies of PAVMs have been done in referral centers for hereditary hemorrhagic telangiectasia, a very different population from that in this study (6). If patients undergoing PFO closure have coexisting intrapulmonary shunts, this might well have significant clinical implications. Further refinements in screening and methodology should one day allow clinicians to readily identify these individuals. As our understanding in this field evolves, PFO closure might not remain as simple an option as it seems today.

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Key Words: patent foramen ovale ■ transcranial Doppler ultrasound ■ intracardiac echocardiography ■ pulmonary arteriovenous malformation.